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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for NexGard Combo (EMEA/V/C/005094/VRA/0012/G)

INN: Esafoxolaner / Eprinomectin / Praziquantel

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

Rapporteur: Andrea Christina Golombiewski

Co-rapporteur: Niels Christian Kyvsgaard

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 64 of Regulation (EU) 2019/6, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 30 October 2024 an application for a group of variations requiring assessment for NexGard Combo.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
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The grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of infections with eye worms (*Thelazia callipaeda*) and immediate tick killing activity against *Ixodes hexagonus*.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

The product NexGard Combo spot-on solution for cats contains the active substances esafoxolaner, eprinomectin and praziquantel, a combination which targets both ectoparasites and endoparasites. NexGard Combo spot-on solution is currently indicated for use in cats with, or at the risk from mixed infections by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time.

With the current grouped variation, the applicant intends to modify the approved treatment against *Ixodes hexagonus* ticks to include immediate efficacy and to add eye worms (*Thelazia callipaeda*) to the list of target nematodes.

With respect to both changes, the product will be administered to the same target species, using the same route of administration and at the same posology that have already been accepted by the CVMP. As such, no concerns in terms of target animal safety, user safety or safety for the environment are to be expected. Therefore, no further assessment is deemed necessary with respect to target animal tolerance, user safety or safety for the environment and it can be concluded that the modification regarding the immediate efficacy against *Ixodes hexagonus* ticks and the introduction of the nematode *Thelazia callipaeda* will not present an unacceptable risk for the animal, the user or the environment.

2.1. Modification of the approved treatment against Ixodes hexagonus ticks

With regard to the activity against *Ixodes hexagonus* ticks, NexGard Combo is currently indicated for persistent killing activity from 7 days to four weeks after treatment. With the current variation procedure, the applicant intends to also demonstrate an immediate killing activity against this tick species and amend the product information accordingly.

To support the proposed inclusion of immediate efficacy against tick infestations with *Ixodes hexagonus*, the applicant provided the results of two pre-clinical dose confirmation studies (studies#1 and #2), of which one study (study #1) has previously been assessed in variation procedure EMEA/V/C/005094/VRA/0007/G.

These studies were designed and conducted largely in line with the relevant guidelines: Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000) and Guideline for the demonstration of efficacy of ectoparasiticides (7AE17a).

Both dose confirmation studies presented were blinded, randomised, negatively-controlled as well as GCP-compliant and were conducted in Europe and South Africa, respectively, to investigate the efficacy of a single topical administration of NexGard Combo against induced infestations of *Ixodes hexagonus* in cats.

In study #1, 16 cats were assigned randomly to treatment or negative control groups and infested under sedation with approximately 40 adult female *Ixodes hexagonus* ticks on day -2 and on day 28.

In study #2, 20 cats were allocated to treatment or negative control groups based on pre-study tick counts and infested under sedation with approximately 40 adult female *Ixodes hexagonus* ticks on day -2.

Both studies used basically the same study model. Animals were sedated and confined within infestation crates (55 cm x 40 cm x 32 cm) to keep closer contact between animals and ticks. Whilst in study #1 this time was set to 30 minutes up to a maximum of two hours, in study #2 this time was extended to about four hours, but not more than six hours.

It is noted that, in both studies, cats were housed individually during the entire study duration, i.e. for 37 days (study #1) and 9 days (study #2), respectively. According to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, with the exception of naturally solitary animals, animals shall be housed in stable groups of compatible animals. In cases where individual housing is justified in accordance with article 33(3), the duration of housing shall be limited to the minimum necessary and visual, auditory, olfactory and/or tactile contact shall be maintained. The CVMP considers that the minimum necessary duration of individual housing would have been between tick infestation and tick collection. Between tick collection and a new infestation, group housing would have been possible, especially in studies with

longer intervals between infestations, such as study #1 where only two infestation timepoints would have allowed for grouping of animals between counting of ticks on day 2 and infestation on day 28. However, cats were randomly allocated to treatment groups and, for group housing, new groups would have had to be formed, which could be considered an additional source of stress for the study animals, in contrast to keeping them individually with visual, auditory and olfactory contact as before. Furthermore, grouping of animals could have led to the transfer of the IVP between the animals by physical contact and grooming resulting in a "common" group exposure to treatment. Consequently, single housing is considered to have been justified.

For study #1, an adequate isolate of *I. hexagonus* collected from the field in 2018 was used for infestation. For study #2, an adequate *I. hexagonus* isolate originating from 2017 was used, which, in accordance with relevant guidelines, was enriched with parasites from field isolates within the recommended time frame of about 6 years.

Mineral oil was administered topically as negative control and cats of the IVP group were topically administered NexGard Combo at the already authorised minimum effective dose of 0.12 ml/kg bodyweight once at D0.

No adverse events occurred during both studies.

Ticks were collected and counted approximately 48 hours after treatment, i.e. on day 2 and in study #1 again on day 30; the numbers of live attached, live free, dead attached and dead free ticks were recorded. Efficacy was based upon a 90% reduction of live attached female ticks for the treated group when compared to the placebo group using arithmetic mean counts.

Sufficient effectiveness of NexGard Combo compared to the untreated control group was demonstrated at day 2 in both studies, with a percentage efficacy of 93.6% in study #1 and 98.6% in study #2. The results were statistically significant and met the requirements of the relevant guidelines, which require an effectiveness of more than 90% compared to placebo.

In summary, the design and results of the two dose confirmation studies provided are adequate to confirm the immediate efficacy against *Ixodes hexagonus* ticks; as such, the proposed changes to the product information are acceptable.

It is noted that another study (study #3) which was submitted in a previous variation application (EMEA/V/C/005094/VRA/0007/G) failed to demonstrate that NexGard Combo had immediate tick killing activity against *Ixodes hexagonus*. In that study, an insufficient efficacy of only 60.5% when compared with the negative control group was observed on study day 2. The applicant explained that the reduced efficacy observed was due to flaws in the study design, more specifically due to the application of Elizabethan collars (E-collars) beyond the time of treatment and this may have had a significant impact on the distribution/absorption of the compound in the initial two days after treatment and thus resulted in reduced efficacy. This argumentation was substantiated by other laboratory studies against *Ixodes* spp. in which the E-collars were removed before treatment and resulted in sufficient efficacy on day 2. Therefore, it can be accepted that the results of study #3 were due to the study conditions.

Different theories might explain why wearing an E-collar could have resulted in the lower efficacy on day 2 after treatment. No additional data has been provided to support either of these theories or to support that the wearing of an E-collar is of little relevance under natural conditions. However, in view of the results of this study, a warning relating to the influence of Elizabethan collars on the efficacy of the product has been included in section 3.4 of the SPC.

In conclusion, taking into account the results of the studies provided, this variation is considered approvable.

2.2. Addition of eye worms (Thelazia callipaeda) to the list of target nematodes

To support the proposed change, the applicant provided two GCP-compliant, randomised, negative controlled and blinded clinical trials (studies #4 and #5), both performed in naturally infected client-owned cats from a region in Italy known to be enzootic for *T. callipaeda* infection in pets. The studies were performed in compliance with VICH GL7 Efficacy of anthelmintics: general requirements. Although in general two dose confirmation studies and one clinical trial are necessary to grant such a claim, for thelaziosis there are no experimental models established in the target species. Therefore, field efficacy studies are the only available option to assess efficacy against *T. callipaeda* (Beugnet *et al*., 2022). Thus, the data of two clinical trials without a laboratory study is considered acceptable to justify the proposed indication regarding treatment of infections with eye worms (*Thelazia callipaeda*).

It is noted that in study #4 cats were treated with NexGard Combo, whereas in study #5 cats were treated with Broadline. The formulations of NexGard Combo and Broadline are very similar in certain relevant aspects. Particularly, the two active substances acting against endoparasites are qualitatively and quantitatively identical, i.e. eprinomectin and praziquantel are contained at the same concentrations. The route of administration (topical) and the target animal species (cat) are also identical between both products. Fipronil and (S)-methoprene in Broadline have been substituted by esafoxolaner in NexGard Combo. Moreover, the solvent and the antioxidant used are qualitatively identical with only a slight quantitative difference due to the amount of esafoxolaner. Because non-interaction between eprinomectin and the other active substances has been demonstrated, the CVMP has already accepted that the efficacy data submitted for Broadline can be extrapolated to NexGard Combo to support nematocidal efficacy (EMEA/V/C/005094/II/0002/G). Considering the above, it is accepted that the results of study GTVS-2018-01 can be taken into account in the context of the current variation for NexGard Combo to add treatment of infections with eye worms (*Thelazia callipaeda*) to the list of already approved nematode infection treatments.

In study #4, 16 naturally infected owner cats (10 males and 6 females) weighing between 2.1 – 5.2 kg and aged between 7 months to 16 years were included, whereas in study #5, 15 naturally infected owner cats (8 males and 7 females) weighing between 1.7 and 6.3 kg and aged between 1 to 15 years were included. In both studies, cats were allocated to the IVP or control group according to the allocation sequence. Cats of the IVP group were treated once topically according to the label instructions (based on body weight ranges). Even if this dosage does not necessarily represent the minimum recommended dose, it can be accepted for clinical trials as it reflects the real use of the product in the field.

Deficiencies have been noted with regard to the blinding: since the cats in the control group remained untreated and thus had a completely dry coat compared to the cats of the IVP group, cats of the IVP group could have been easily detected by the changes of the hair coat at the application site. This is also described in section 4.6 of the SPC for Broadline, where it is stated that a temporary clumping and spiking of the hair is commonly observed after application. Therefore, it can be assumed that the application site of the oily formulation (even if the blinded persons were not present during the treatment) would identify cats of the IVP group/control group in some cases. However, it is considered unlikely that any potential unblinding arising from the use of an untreated control group would have biased the primary efficacy outcome findings, considering that the approach to determining presence/absence of parasite infection was based on an objective (as opposed to a subjective) parameter measurement, i.e. proportion of cats free of *T. callipaeda* as assessed by the flushing of the conjunctivae of both eyes for the confirmation of parasite presence and recovery.

The study groups (7 or 8 cats per group) were adequately infected with at least one eye worm in at least one eye per cat. In line with the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010), at least six cats per group have to be adequately infected in order to calculate significant differences between groups. Therefore, the number of 7 - 8 animals per study group is sufficient. The primary endpoint was the proportion of worm-free cats of the IVP group compared to the control group in both studies. In study #4, the following secondary endpoints were compared between the study groups: presence of clinical signs caused by eye worm infestation and number of worm counts. The cats were classified as worm-free or not worm-free based on ocular assessment (D7, 14) and flushing of the conjunctival fornix of both eyes with ~5 ml 0.9% saline solution (D14) to collect and count ocular worms, which represents an adequate diagnostic method.

In both studies at D14, 100% efficacy was calculated, i.e. no cats of the IVP group harboured any eye worm, whereas cats of the control group were significantly higher infected with an average of 2 worms per cat. At study day 7, efficacy in cats of the IVP group was 100% and 75% in study #4 and #5, respectively. Sufficient efficacy (≥90%) can therefore be confirmed from 14 days after treatment at the earliest. Although the clinical signs of thelaziosis improved only by 12.5% on D7, they improved by 62.5% on D14 in the IVP group in study #4, while there was a worsening of the symptoms in the control group during the course of study. Since in study #5 cats in both study groups were treated with concomitant medications such as antibiotics or NSAIDs that reduced or removed signs of ocular infections, clinical symptoms caused by eye worm infestation were not evaluated in this study.

No adverse events were observed in any study group during the studies, with the exception of those caused by the eye worm infections themselves.

Amendments and deviations occurring during the studies did not affect the validity of the study results.

In summary, the design and results of the provided studies are adequate to confirm the efficacy for the proposed treatment of infections with eye worms (*Thelazia callipaeda*). Therefore, this variation is considered approvable.

3. Benefit-risk assessment of the proposed change

NexGard Combo is indicated for the treatment of cats with, or at risk from, mixed infections by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time. The active substances are esafoxolaner (the (S)-enantiomer of afoxolaner which belongs to the isoxazoline class, active against arthropods), eprinomectin (a member of the macrocyclic lactone class of endectocides, covering nematodes, but also mites) and praziquantel (a synthetic isoquinoline-pyrazine derivative with activity against tapeworms). The product is presented as spot-on solution.

The proposed grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of infections with eye worms (*Thelazia callipaeda*) and immediate tick killing activity against *Ixodes hexagonus*.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of the variation to the marketing authorisation of NexGard Combo is a) the immediate efficacy against *I. hexagonus* ticks, and b) the addition of eye worms (*Thelazia callipaeda*), to the list of the nematode infections that can be treated with the veterinary medicinal product. The proposed changes were substantiated by a number of laboratory studies and clinical trials conducted with an acceptable standard.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety (user, environmental, target animal) remains unaffected by this variation.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, target animal safety.

The product has been shown to be efficacious for the immediate killing activity against *I. hexagonus* ticks and for the treatment of infections with eye worms (*Thelazia callipaeda*).

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for NexGard Combo can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of infections with eye worms (*Thelazia callipaeda*) and immediate tick killing activity against *Ixodes hexagonus*.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of these variations, sections 3.2, 3.4, 3.9 and 4.2 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.